

# A nationwide population-based prospective study of cirrhosis in Iceland

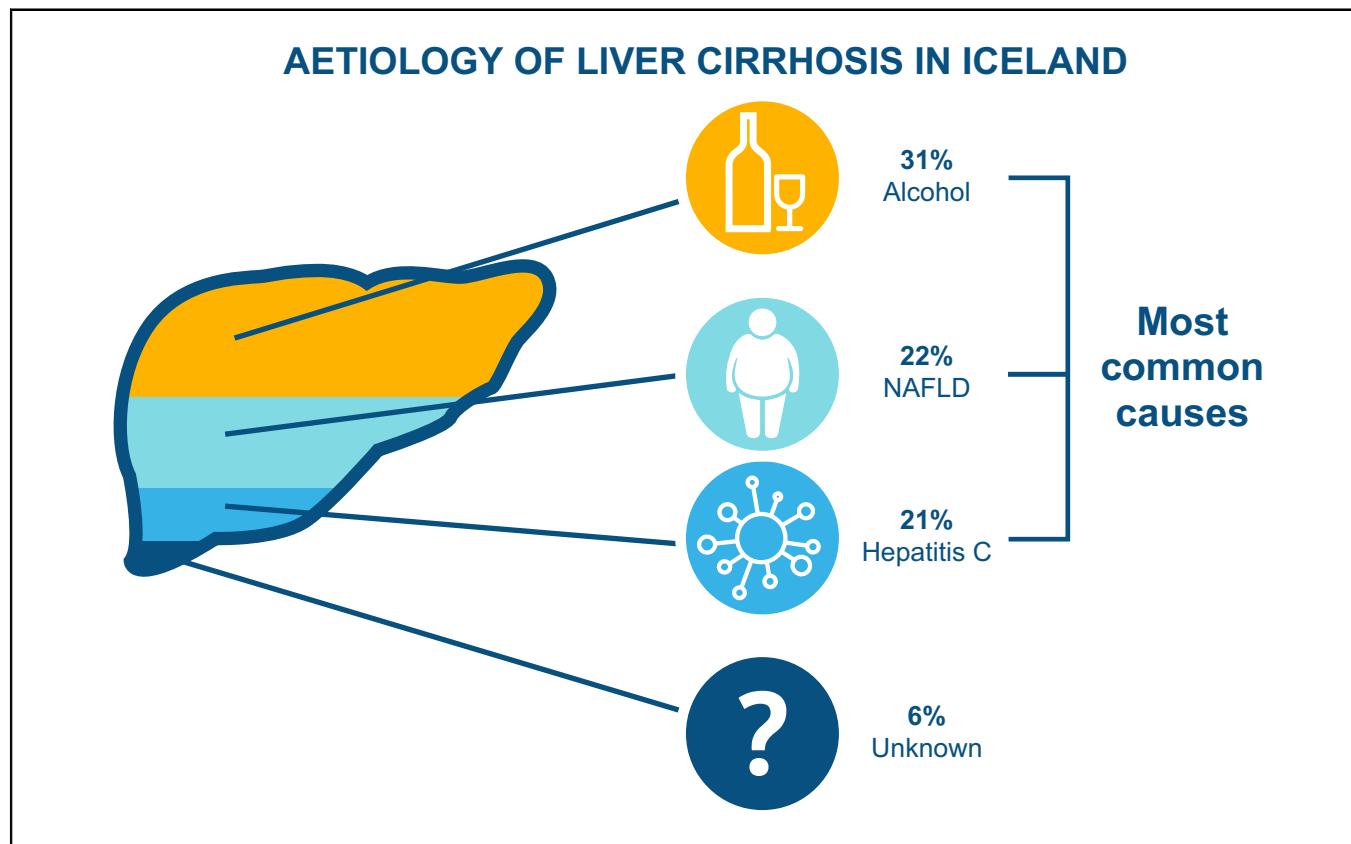
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## Graphical abstract



## Highlights

- The incidence of cirrhosis in Iceland has been the lowest among western countries.
- In this nationwide prospective study, all patients diagnosed with cirrhosis of the liver in Iceland over a period of 5 years were included.
- The incidence of cirrhosis had increased 3-fold compared with a study 10 years earlier owing to increased alcohol consumption, obesity, and hepatitis C.
- With thorough investigations a specific cause for cirrhosis could be found in 94% of patients.

## Lay summary

In a nationwide population-based study from Iceland, including all patients diagnosed with cirrhosis of the liver over a period of 5 years, we found the incidence of new cases had increased 3-fold compared with a previous study 20 years ago. The increase is attributable to increased alcohol consumption, an epidemic of diabetes and obesity, and infection with the hepatitis C virus. Furthermore, we found that with thorough investigations, a specific cause for cirrhosis could be found in 94% of patients. Patients with cirrhosis frequently die of liver cancer and other complications related to their liver disease.



# A nationwide population-based prospective study of cirrhosis in Iceland



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**Background & Aims:** The incidence of cirrhosis in Iceland has been the lowest in the world with only 3 cases per 100,000 inhabitants. Alcohol consumption has almost doubled in Iceland from 1980 to 2016. Obesity has also risen and hepatitis C virus has spread among people who inject drugs in Iceland. The aim of this study was to evaluate the effects of these risk factors on the incidence and aetiology of cirrhosis in Iceland.

**Methods:** The study included all patients diagnosed with cirrhosis for the first time during 2010–2015. Diagnosis was based on liver histology or 2 of 4 criteria: cirrhosis on imaging, ascites, varices, and/or elevated INR.

**Results:** Overall, 157 patients were diagnosed, 105 (67%) males, mean age 61 years. The overall incidence was 9.7 cases per 100,000 inhabitants annually. Alcohol was the only underlying cause in 48/157 (31%), non-alcoholic fatty liver disease (NAFLD) in 34/157(22%), and alcohol and hepatitis C together in 23/157(15%) were the most common causes. Only 6% of patients had an unknown cause of cirrhosis. Upon diagnosis, the median model for end-stage liver disease score was 11 (IQR 8–15), 53% were of Child-Pugh class A whereas 61 (39%) had ascites, 11% encephalopathy, and 8% variceal bleeding. In all, 25% of deaths were from HCC and 25% from liver failure.

**Conclusion:** A major increase in incidence of cirrhosis has occurred in Iceland associated with increases in alcohol consumption, obesity, and hepatitis C. In a high proportion NAFLD was the aetiology and very few had unknown cause of cirrhosis. The highest death rate was from HCC.

**Lay summary:** In a nationwide population-based study from Iceland, including all patients diagnosed with cirrhosis of the liver over a period of 5 years, we found the incidence of new cases had increased 3-fold compared with a previous study 20 years ago. The increase is attributable to increased alcohol consumption, an epidemic of diabetes and obesity, and infection with the hepatitis C virus. Furthermore, we found that with thorough investigations, a specific cause for cirrhosis could be found in 94% of patients. Patients with cirrhosis frequently die of liver cancer and other complications related to their liver disease.

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## Introduction

Liver cirrhosis, an end stage of multiple chronic liver disorders, is a major health problem worldwide. The patterns and trends in cirrhosis mortality and incidence are largely attributable to differences and changes in the 3 major recognised causes of this disease, that is HBV and HCV infection, alcohol consumption, and non-alcoholic fatty liver disease.<sup>1</sup> Incidence and mortality has been decreasing in many southern European countries but on the rise in eastern European countries and in the UK.<sup>2,3</sup> Most

countries report only mortality based on death certificates. Published studies are almost only retrospective and often refer to defined geographical areas such as cities.<sup>4</sup> The incidence of cirrhosis in Iceland has been the lowest among western countries. In a retrospective study for the time period of 1994–2003 the incidence was 3.3 patients per 100,000 inhabitants annually.<sup>5</sup> The main reasons for the low incidence was considered relatively low *per capita* alcohol consumption as well as low prevalence and a late introduction of hepatitis C into the Icelandic i.v. drug use population.<sup>5</sup> The incidence of cirrhosis has been found to be more than 4–5 times higher in Sweden and Norway<sup>5,6</sup> and almost 10 times higher in Denmark.<sup>7</sup>

In recent years, a significant change in the epidemiology of major risk factors for cirrhosis has occurred in Iceland. *Per capita* alcohol consumption increased from 4.3 L per inhabitant older than 15 years in 1980, to 7.5 L in 2016.<sup>8</sup> Hepatitis C has become a

Keywords: Cirrhosis; Aetiology of cirrhosis; Incidence of cirrhosis; Alcohol; NAFLD; Hepatitis C.

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significant health problem<sup>9</sup> and there is an increase in diabetes and obesity.<sup>10</sup>

In a systematic review of the natural history studies of cirrhosis by D'Amico *et al.*,<sup>11</sup> 'good' quality studies were defined by 5 major quality criteria: (a) inclusion of consecutive patients, (b) relevant baseline patient characteristics (age/sex, aetiology of cirrhosis, Child-Pugh and model for end-stage liver disease [MELD] scores), (c) length of follow-up reported, (d) clinically important variables for prognosis included, (e) number of deaths reported. The current study set out to include all these major quality criteria. Furthermore, the benefits of a population-based approach and rigorous diagnostic work-up was intended to improve the generalisability of the results and avoid bias. To our knowledge, this is the first study of the incidence of cirrhosis including the entire population of a country.

The aims of this study were to assess the incidence and aetiology of cirrhosis in Iceland and to evaluate the prognosis of cirrhosis with respect to different aetiologies.

## Materials and methods

### Patients and inclusion criteria

This was a prospective study. Every patient diagnosed with cirrhosis in Iceland (population of 330,000) from 1 March 2010 to 28 February 2015 were eligible and enrolled at the time of diagnosis.

In Iceland, the majority of patients with advanced liver disease are diagnosed and/or managed at Landspítali-National University Hospital of Iceland (LUH), Reykjavík, where at least 95% of patients with liver disease are hospitalised. Few patients are diagnosed in Akureyri District Hospital. In rare exceptional cases diagnosis was suspected in other institutions and these patients were referred to the National University Hospital.

### Patient recruitment/identification

A letter informing on the planned study was sent out at the beginning of 2010 to gastroenterologists, general surgeons, radiologists, and pathologists in Iceland. They were encouraged to refer all patients suspected of cirrhosis to the study hepatologists based at LUH. To further facilitate early referral to LUH hepatologists, and to ensure that patients were not missed, with regular intervals, all patients receiving at least 1 diagnosis indicating liver fibrosis or cirrhosis, chronic liver disease, or complications possibly caused by cirrhosis (International Classification of Diseases 10th edition) were identified by searching electronic medical records and computerised diagnosis databases on a regular basis during the study period to avoid missing any recent diagnoses of cirrhosis. Pathology and autopsy reports were also regularly searched and screened for cirrhosis. Information on cause of death was obtained from medical records and, when the patients died outside the hospital, the Icelandic cause of death register.

### Data collection

The majority of patients (143 [91%]) were interviewed by 1 of the authors who are clinical hepatologists (SO, OMB, or ESB). The rest were mainly seen in the other main hospital in Iceland, Akureyri. Upon examination of referral history and medical records, each patient was thoroughly evaluated to determine if they had previously received a diagnosis of cirrhosis. Information was obtained on general health, history of liver diseases, risk factors for liver disease such as diabetes, obesity, alcohol use, drug use

(including i.v.), and family history of liver disease. Medications were documented. For deceased patients who died shortly after diagnosis in hospital, information was obtained from medical records.

Findings from physical examination, such as height, weight, BMI, and the presence of ascites (confirmed by ultrasound), hepatic encephalopathy, or variceal bleeding at diagnosis were recorded.

The following laboratory analyses were performed: complete blood count, platelets, creatinine, bilirubin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transpeptidase, INR, albumin, serum iron, transferrin iron-binding capacity, ferritin, anti-nuclear antibody, smooth muscle antibody, anti-mitochondrial antibody, ceruloplasmin,  $\alpha$ -1-antitrypsin, HBsAg, anti-HBC core, and anti-HCV (HCV RNA if positive). In addition, a blood sample was stored for a possible later genetic study. All patients underwent imaging studies (ultrasound, computed tomography [CT] scans, magnetic resonance imaging) and upper endoscopy was performed to evaluate the presence of varices. Patients were divided into those with compensated and decompensated cirrhosis. Compensated cirrhosis was defined by absence of gastrointestinal bleeding, ascites (confirmed by ultrasound or CT), jaundice (serum bilirubin  $>50 \mu\text{mol/L}$ , normal  $<25$ ), or symptomatic encephalopathy on physical examination. Decompensated cirrhosis was defined as presence of any of these abovementioned complications.

Liver biopsies, undertaken when clinically indicated, mostly in patients with Child Pugh A were examined by the same experienced pathologist (J.G.J.).

The MELD score<sup>12</sup> and Child-Pugh score<sup>13</sup> were calculated.

All living patients signed an informed consent for participation in the study.

For a patient to be eligible in this study they had to fulfil either (i) biopsy-proven cirrhosis or (ii) at least 2 of the following 4 criteria: medical imaging indicating cirrhosis, elevated INR, if it could not be attributed to any other cause such as treatment with vitamin K antagonists, ascites, or gastroesophageal varices (that could not be attributed to any other cause).

In patients without history of excess alcohol consumption ( $<14$  units of alcohol per week for women and  $<21$  for men), the aetiology of cirrhosis was considered to be non-alcoholic fatty liver disease (NAFLD) rather than cryptogenic if the following criteria were fulfilled: (i) liver biopsy (at any point) demonstrating fatty liver disease or (ii) without liver biopsy a history of diabetes mellitus and/or BMI  $\geq 30$  before cirrhosis diagnosis. Exclusion of other specific aetiologies was also required to categorise NAFLD as the aetiology of cirrhosis.

Patients could have more than 1 cause of cirrhosis. If a patient with HCV also had a history of alcohol abuse, both disorders were registered as the aetiology. The patients were followed for the documentation of development of hepatocellular carcinoma (HCC) and transplantation and death or to the end of September 2019. The study protocol did not include longitudinal follow-up for development of other complications of cirrhosis.

### Statistical analysis

Data were processed using Microsoft Office Excel 2013 (Microsoft Corporation, Redmond, WA, USA), R-project (R Foundation for Statistical Computing, Vienna, Austria), and STATA version 13.1 (Stata Corporation, College Station, TX, USA). Results are presented as means (SD) as well as medians and IQR for non-normally distributed data, and other statistics with CIs.

**Table 1.** Patient characteristics at the time of diagnosis.

	<b>Men</b>	<b>Women</b>	<b>Total</b>
No. of patients, n (%)	105 (67)	52 (33)	157
Age, years mean (SD)	60.8 (14.6)	61.9 (15.4)	61.1 (14.9)
ALD vs. NALD	56.5 (10.7) vs. 65.6 (16.9)	63.6 (9.85) vs. 61 (17.5)	58 (11) vs. 63.6 (17.2)
Aetiology, n (%)			
Alcohol	36	13	49 (31)
Alcohol + HCV	21	2	23 (15)
HCV	6	3	9 (6)
NAFLD	24	10	34 (22)
PBC	2	6	8 (5)
AIH	0	6	6 (4)
Other	10	9	19 (12)
Unknown	6	3	9 (6)
Ascites, n (%)	42	19	61 (39)
Variceal bleeding, n (%)	10	3	13 (8)
Hepatocellular carcinoma, n (%)	11	0	11 (7)
Any sign of decompensated cirrhosis, n (%)	48 (46)	30 (58)	78 (50)
Child-Pugh class, n (%)			
A	55	24	79/148 (53)
B	31	16	46/148 (31)
C	16	7	23/148 (16)
MELD score, median (IQR)	11 (8–15)	10.3 (8–15.3)	11 (8–15)

AIH, autoimmune hepatitis; ALD, alcoholic liver disease; MELD, model for end-stage liver disease; NAFLD, non-alcoholic fatty liver disease; NALD, non-alcoholic liver disease; PBC, primary biliary cirrhosis.

The incidence of cirrhosis was calculated per 100,000 person-years, stratified by year of diagnosis and sex and the age-standardised incidence was calculated using the 1976 European standard population.<sup>14</sup> We plotted the age-standardised incidence over time.

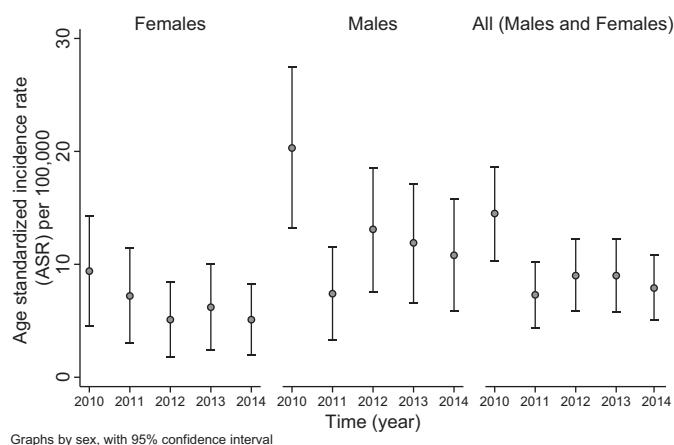
For survival analysis, where death was the endpoint, we calculated and plotted the non-parametric cumulative incidence function (CIF) over time, unstratified, and stratified by aetiology and sex. For the former, we fitted a null-model competing-risks regression. We also plotted the CIF derived from the first competing-risks regression analysis outlined below. This CIF was evaluated at the means of the variables in the aforementioned analysis and also presented by aetiology alcohol (vs. other), and by sex.

If individuals did not reach the endpoint, they were censored at the end of the study period; for individuals who underwent transplantation, this was considered a competing risk from the date of transplantation. Also, we assessed the effect (and

adjusted for) a number of factors on the risk of death with competing-risks regression analysis.<sup>15</sup> The variables included in the analysis were aetiology alcohol vs. other (non-alcoholic aetiology), age, sex, and MELD score. We plotted the CIFs mentioned above and performed a competing-risks regression per each of the following: all individuals, and only individuals with HCC (none had undergone liver transplantation). For non-parametric CIF all 157 individuals were evaluated. For competing risks regression analysis and adjusted CIF, 8 were excluded individuals due to a lack of MELD score at diagnosis. Thus, the analyzed groups and their corresponding observations were: all individuals ( $n = 149$ ), and those with HCC ( $n = 22$ ).

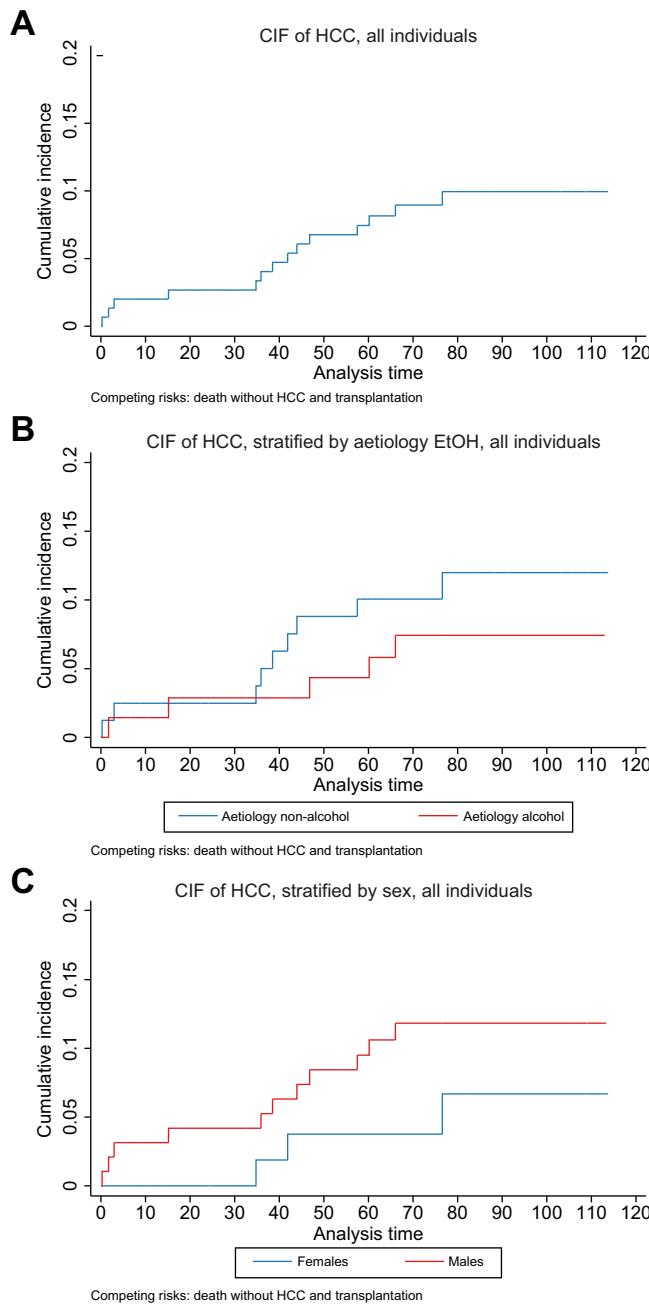
Entry time was at diagnosis of cirrhosis for all individuals; in the case of only individuals with HCC entry time was at diagnosis of HCC. We tested the proportionality of subhazards assumption by interacting the coefficients of the variables of the regressions with time, which indicated that the competing-risks regressions were adequate for all individuals, but indicated non-proportionality for the regression of only individuals with HCC.

Following the guidelines by Lau *et al.*,<sup>16</sup> when there was an indication of non-proportionality this was acknowledged and

**Fig. 1.** Age standardised rates for all patients on the right, for females on the left, and males in the middle, during the study period.**Table 2.** Other aetiologies of cirrhosis.

	<b>Men</b>	<b>Women</b>	<b>Total</b>
Hepatitis B	2	2	4
Hemochromatosis	3	0	3
Methotrexate	1	1	2
Familial intrahepatic cholestasis	2	0	2
Cystic fibrosis	0	2	2
Amiodarone	1	0	1
AIH + PBC overlap	0	1	1
Budd-Chiari	0	1	0
Secondary biliary cirrhosis	0	1	1
Hepatitis B + Hepatitis C	1	0	1
PBC/PSC overlap	0	1	1
Total	10	9	19

AIH, autoimmune hepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis.



**Fig. 2. Non-parametric cumulative incidence function of developing HCC from diagnosis of cirrhosis.** The endpoint was developing HCC: death without HCC and transplantation were considered competing events. The curves are presented by (A) all individuals, unstratified (blue line); (B) all individuals, stratified by aetiology alcohol (red line) vs. other (blue line); (C) all individuals, stratified by sex male (red line) and female (blue line). CIF, cumulative incidence function; HCC, hepatocellular carcinoma.

subhazard ratios (SHRs) reported, as this is the weighted average over the follow-up. In the current study, data are presented for the whole nation of Iceland during the study period. We report CIs if generalising these results to a supranational region<sup>17</sup> (e.g. the Nordic countries) could be considered.

Non-parametric CIF was plotted and calculated where HCC was the endpoint ( $n = 14$ ). If individuals did not reach the endpoint, they were censored at the end of the study period;

**Table 3. Causes of death.**

	Male	Female	Total
Liver failure	13	6	19 (25)
HCC	17	2	19 (25)
Variceal bleeding	2	0	2 (3)
Another malignancy	6	1	7 (9)
Infections	6	6	12 (16)
Other*	11	7	18 (23)
	55	22	77

Data are presented as n or n (%). \*Non-liver related death: cardiac arrest/myocardial infarction ( $n = 7$ ), brain/subdural haematoma haemorrhage ( $n = 3$ ), kidney failure ( $n = 2$ ), trauma ( $n = 2$ ), toxic effects of alcohol ( $n = 1$ ), Alzheimer's disease ( $n = 1$ ), Parkinson's disease ( $n = 1$ ), and unclear cause of death ( $n = 1$ ). HCC, hepatocellular carcinoma.

death without HCC and transplantation were considered competing events. Entry time was at the diagnosis of cirrhosis.

### Ethics

This study was approved by the Bioethics Committee of Iceland (VSN-09-158) and Data Protection Authority of Iceland.

## Results

### Incidence

A total of 157 patients were diagnosed with cirrhosis during the study period. Clinical characteristics of the patients are shown in Table 1. The mean age was approximately 61 years and males comprised two-thirds of the patients (Table 1). The overall age standardised incidence rate for the study period was 9.5 per 100,000 person-years (95% CI, 8.0–11.0); 12.6 for males (95% CI, 10.1–15.1) and 6.6 for females (95% CI, 4.8–8.3). The incidence was significantly higher during the first study year, 14.4 per 100,000 person-years but remained stable thereafter (Fig. 1).

### Causes of cirrhosis

Alcohol was the most common cause of cirrhosis, alone (31%) or in combination with hepatitis C (15%). NAFLD was found to be the aetiology in 22% of cases and 20% hepatitis C of whom the majority also had alcohol as a risk factor for cirrhosis (Table 1). Alcohol and HCV were more common among males than females (Table 1). More than 1 cause of cirrhosis was found among 24 patients. A variety of other causes of cirrhosis were observed of whom hepatitis B was the most frequent of uncommon causes (Table 2). The most common method of diagnosis was by liver biopsy, which was undertaken in 77 patients (49%).

### Presenting complications and stage of disease

The most common complication of cirrhosis at diagnosis was ascites in 61 patients (39%) (Table 1). Of 148 patients with known Child-Pugh class, approximately 50% were of class A, 31% class B, and 16% class C (Table 1). The median MELD score was 11.9 with no difference between males and females (Table 1).

### HCC

At diagnosis of cirrhosis, 8 (5%) patients were concomitantly diagnosed with HCC with an additional 14 patients diagnosed during follow-up (3 patients within 3 months from the diagnosis of cirrhosis) with a total of 22/157 (14%) with HCC. Among males, 19/105 (18%) had HCC compared with only 3/52 (6%) of females. Risk of HCC was highest in patients with NAFLD-induced cirrhosis occurring in 8/34 (24%) of patients. The risk of HCC was relatively low in patients who had alcohol alone as a cause of

**Table 4.** Subhazard ratios of death without liver transplantation from competing-risks regression analysis.

	Subhazard ratio, all individuals n = 149	95% CI
Age	1.05	1.03–1.07
Cause (alcohol)	0.69	0.37–1.29
Male sex	2.75	1.52–5.01
MELD	1.19	1.12–1.26
	Subhazard ratio, HCC individuals (non-proportional) n = 22	95% CI
Age	1.01	0.97–1.05
Cause (alcohol)	0.89	0.21–3.78
Male sex	1.75	0.26–11.77
MELD	1.15	0.90–1.46

HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease.

cirrhosis, occurring in 4/49 (8%), and also in patients with alcohol and HCV as a cause of cirrhosis (17%). Two of 3 patients with haemochromatosis developed HCC. Of 22 patients with HCC, 19 (86%) died during follow-up. Cumulative risk of developing HCC with death and liver transplantation as competing risks, from cirrhosis diagnosis, was 0.074 at 5 years, as shown in Fig. 2.

### Survival and causes of death

The median follow-up was 61 (IQR 14–84) months. Cumulative incidence function (non-parametric) of death without liver transplantation, at 1 year was 0.23, and 0.79, for all individuals, and only individuals with HCC, respectively (Fig. S1A,B). A total of 5 (3.2%) patients underwent liver transplantation at a median 13 (range 6–81) months following diagnosis. Approximately 68% deaths were considered directly related to their liver disease, such as because of liver failure, HCC, and variceal bleeding, or indirectly because of infections (Table 3). Interestingly, 25% of deaths were due to HCC (Table 3). We cannot exclude the possibility that some of the patients who died and had HCC also had some degree of liver failure. None of the patients who died from other causes as listed in Table 3 had HCC. Only 3% of patients died from variceal bleeding. Men had higher (non-parametric) cumulative incidence of death without liver transplantation than women (Fig. S1E,F). Cumulative incidence (non-parametric) of death without liver transplantation in alcoholic induced cirrhosis and non-alcoholic induced cirrhosis were similar overall (Fig. S1C,D).

A multivariate competing-risks regression analysis using biochemical and clinical parameters found 4 factors with SHRs of death without liver transplantation indicating worse prognosis. These were age, non-alcoholic aetiology, male sex, and MELD score (Table 4). The CIF of death without liver transplantation derived from this competing risks regression analysis with these 4 factors is shown in Fig. 3. After adjustment, the CIF of death without liver transplantation at 1 year was 0.18 and 0.81, for all individuals and only individuals with HCC, respectively (Fig. 3A,B). After adjustment, the cumulative incidence of death without liver transplantation was higher for non-alcoholic induced cirrhosis (Fig. 3C,D). After adjustment, men had higher cumulative incidence of death without liver transplantation than women (Fig. 3E,F).

These aforementioned results/SHRs of death without liver transplantation indicate the direction of the effects on the risk, but not their magnitudes as indicated previously.<sup>18</sup> Also, when looking at only individuals with HCC (Table 4), the SHRs for this competing-risks regression change with time, (i.e. they are non-proportional); the results reported are the weighted average over follow-up.<sup>16</sup>

### Discussion

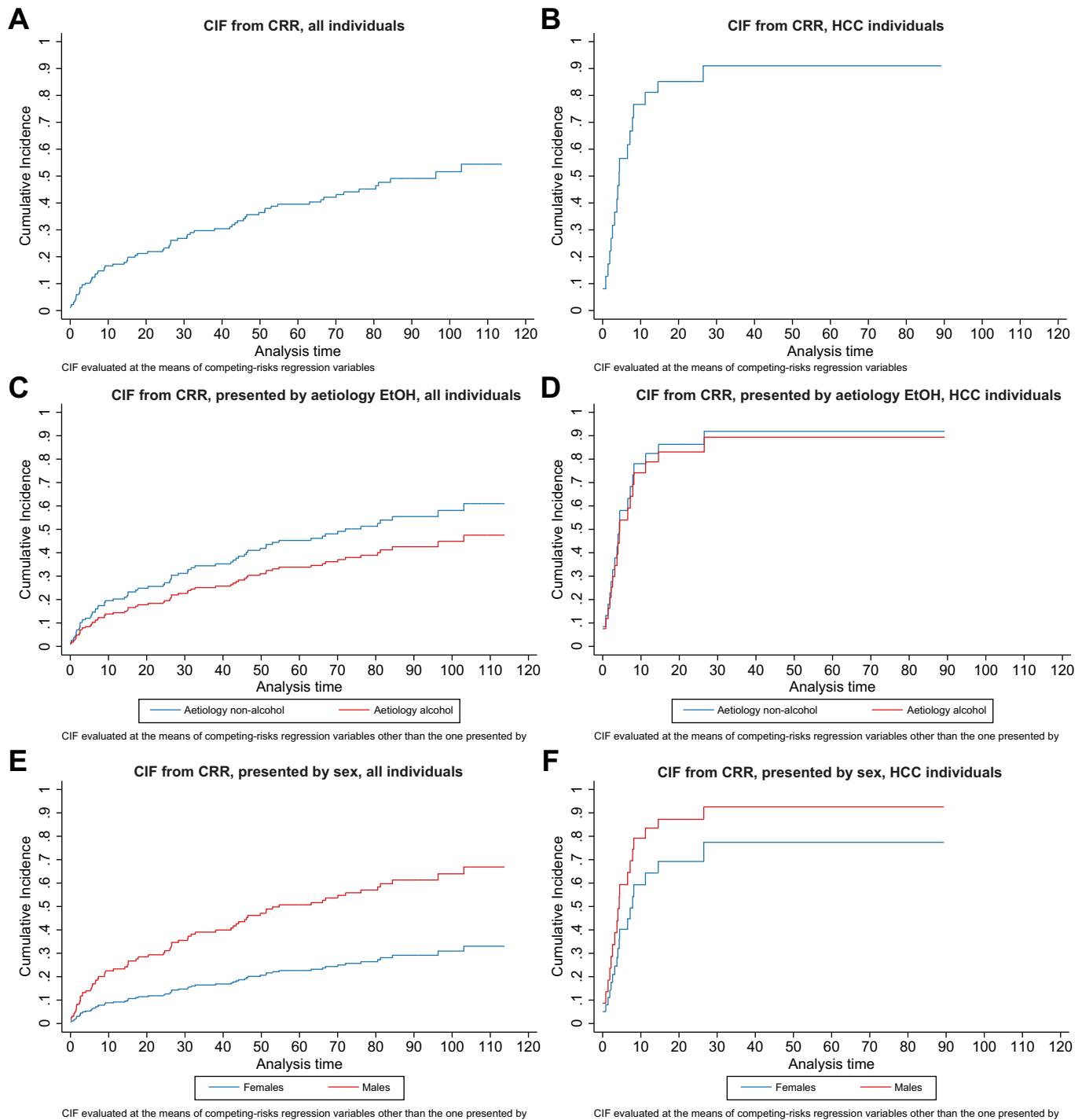
This nationwide study demonstrated a major increase in the incidence of cirrhosis in Iceland. The dominating causes of cirrhosis were alcohol, NAFLD, and hepatitis C. The current study included all major quality criteria for ‘good’ natural history studies of cirrhosis presented by D’Amico *et al.*<sup>11</sup> In a systematic review of natural history studies, only one of the 118 retrospective studies included fulfilled all these criteria.<sup>18</sup>

### Incidence of liver cirrhosis

The crude incidence rate during the 5-year period 2010–2015 was 9.7 per 100,000 inhabitants which compares with a retrospective Icelandic study from 1994 to 2003 where the incidence was only 3.3.<sup>5</sup> The incidence was highest in the first year of the study. It is likely that the increased awareness and knowledge about cirrhosis following the widely disseminated information on the study among colleagues, might have led to the identification of more patients (who may have had signs of cirrhosis for some time) during the first year. Therefore, the subsequent years are likely to represent the true incidence more accurately.

Unfortunately, the data on the epidemiology of cirrhosis globally are very limited. There are no nationwide databases on the causes of cirrhosis and incidence. The limited statistics kept by health authorities focus on hospital discharge registries and cause of death registries. However, apart from the current study few retrospective studies on incidence of cirrhosis have been carried out recently, almost exclusively in the Nordic countries, Sweden, Norway, and Denmark.<sup>4–7,19–21</sup> In spite of the increase over recent years, the incidence remains low in Iceland.

In retrospective studies from Gothenburg (1994–2003)<sup>5</sup> and a more recent study from southern Sweden (2001–2011) the incidence was 15.3 and 14.1, respectively.<sup>19</sup> Contrary to the results of the current study, no increase in incidence was observed in Sweden.<sup>19–21</sup> A study from Norway showed that the incidence was 13 cases per 100,000 inhabitants annually between 1999 and 2004.<sup>6</sup> Strikingly higher incidence of 33 was reported by a study in the defined population of Funen, Denmark between 1996 and 2006.<sup>7</sup> The incidence appears to be stable in Sweden and Norway, whereas it is increasing in Iceland and Denmark.<sup>4</sup> From the available data it can be concluded that significant differences exist in the Nordic countries in the epidemiology of cirrhosis. The drawback of all these previous studies is the retrospective design. Other studies outside the Nordic countries show that cirrhosis mortality has been decreasing in Southern European countries such as Spain, Italy, and France and increasing in many eastern European countries.<sup>2,3</sup> In the UK annual incidence rose by 25%, increasing from approximately 12 to 17 per 100,000 person-years from 1992 to 2001.<sup>22</sup> It is likely



**Fig. 3. Cumulative incidence function of death without liver transplantation from CRR analysis of individuals with cirrhosis.** CIF of death without liver transplantation was derived from a CRR analysis that included the variables age, aetiology alcohol vs. other, sex, and MELD severity. The CIF curve was evaluated at the means of the variables in said analysis, and also presented by aetiology alcohol (vs. other) and by sex. Columns from left to right correspond to all individuals (A,C,E), and only individuals with HCC (B,D,F). Rows from top to bottom correspond to: (A,B) CIF evaluated at the means of all the variables (blue line); (C,D) CIF presented by aetiology alcohol (red line) vs. other (blue line) and at the means of the rest of the variables; (E, F) CIF presented by sex – male (red line) and female (blue line) and at the means of the rest of the variables. The endpoint was death and transplantation was considered a competing event. None of HCC individuals underwent transplantation. CIF, cumulative incidence function; CRR, competing-risks regression; HCC, hepatocellular carcinoma.

that this increased incidence is related at least partly to increased alcohol consumption. Previous studies on changes in incidence and mortality from cirrhosis have demonstrated relationship with trends in alcohol consumption.<sup>23</sup> *Per capita* alcohol consumption in Iceland has increased from 4.3 L per inhabitant older than 15 years in 1980 to 7.5 L in 2016.<sup>8</sup> The increase in the incidence of cirrhosis in Iceland probably reflects not only increased alcohol consumption, but also increases in other risk factors such as HCV, obesity, and diabetes mellitus type II.

### Aetiology of cirrhosis

Alcohol was the sole cause of cirrhosis in 31% of cases and in combination with hepatitis C in 15%. Thus, alcohol was the cause or an important contributing factor of cirrhosis in 46% of patients in the current study compared with 32% in a previous study for the period 1994–2003.<sup>5</sup>

A total of 32 (20.4%) patients had HCV infection, in the majority of cases this was in combination with alcohol as a cause of cirrhosis. This is remarkably similar to the recent study from southern Sweden where 21.7% of the patients had HCV.<sup>19</sup> In a previous Icelandic study only 3% of patients had HCV infection.<sup>5</sup> The increasing importance of HCV as a cause of cirrhosis was to be expected because of the late spread of the virus among people who inject drugs in Iceland<sup>9,24</sup> and the long incubation time from infection to development of cirrhosis, generally 20–30 years.<sup>25</sup> The combination of increased alcohol consumption and increased prevalence of HCV during the same period in Iceland is of a particular concern as alcohol is known to potentiate the risk of cirrhosis among patients with HCV.<sup>25</sup>

NAFLD was the cause of cirrhosis in approximately 22% of patients. In the previous retrospective Icelandic study only 5% of patients were considered to have NAFLD.<sup>5</sup> Only 3% and 4% of patients were considered to have NAFLD as the cause of their cirrhosis in studies on cirrhosis from Norway and Sweden, respectively.<sup>6,17</sup> Similarly, in a recent study from Germany only approximately 1% of patients with cirrhosis were thought to have NAFLD as the aetiology of cirrhosis.<sup>22</sup> These differences are probably explained by the prospective approach of the current study, an increased awareness of NAFLD as a cause of cirrhosis, and differences in definitions. In the Swedish study<sup>19</sup> the aetiology was categorised as NAFLD only if the clinicians set out the diagnosis and in the German study only if steatosis was seen on ultrasound with exclusion of other aetiologies.<sup>26</sup> The missing data and uncertainties of the medical history are among many drawbacks of retrospective studies.<sup>19,26</sup> In the current study, predetermined criteria were used to assess this potential aetiology incorporating both presence of steatosis and features of metabolic syndrome. In the previous Icelandic study, 20% of patients were categorised as ‘cryptogenic’<sup>5</sup> and it is likely that a significant proportion of these patients had NAFLD. However, the main explanation for the increased incidence of NAFLD-associated cirrhosis is probably the changing epidemiology of the main risk factors in Iceland with an epidemic of obesity and diabetes mellitus developing in recent years. In 1967 the prevalence of obesity ( $BMI \geq 30$ ) was 9% among males and 11% among females (age 45–64 years). In 2007 the prevalence was 27% and 23% among males and females, respectively. During the same period the prevalence of diabetes has doubled among males and increased by 50% among females.<sup>10</sup> The results of the current study are in line with other studies on the epidemiology of NAFLD/non-alcoholic steatohepatitis (NASH) showing a large increase in NAFLD-induced liver cirrhosis.<sup>27</sup> NASH has been

shown to be the second leading aetiology of liver disease among patients awaiting liver transplantation in the USA.<sup>28</sup> It is conceivable that alcohol as an aetiology might be overestimated as the cause of cirrhosis in retrospective studies<sup>5–7,18–21,26,29</sup> and probably a large underestimation of NAFLD/NASH as the cause of cirrhosis as the results of the current study suggest. Primary biliary cirrhosis (PBC) was the cause of cirrhosis in 5% of the patients of the present study which was almost twice as high (2.6%) as the proportion in the recent Swedish cohort of patients with cirrhosis.<sup>18</sup> This is in line with a recent study showing that the incidence and prevalence of PBC in Iceland is among the highest in the world.<sup>30</sup> By contrast, during the study period only 1 patient was reported to have primary sclerosing cholangitis (PSC) in an overlap with PBC as a cause of cirrhosis. A recent study showed a much lower incidence of PSC in Iceland<sup>31</sup> compared with other Nordic countries, where the incidence of PSC is among the highest worldwide.<sup>32,33</sup> In the current study, only 6% were found to have cryptogenic cirrhosis which is much lower than in other cohorts with cirrhosis.<sup>5–7,18–21,26,29</sup> This is most likely because of thorough scrutinisation of potential aetiologies and probably reflects the fact that most patients in other previous cohorts with cirrhosis classified as cryptogenic are attributable to NAFLD/NASH. Thus, it seems that if detailed diagnostic criteria are used, very few patients have cryptogenic cirrhosis.

### Complications of the liver cirrhosis

Approximately 50% of patients were of Child-Pugh class A. This is a relatively high proportion of Child-Pugh class A patients in a cohort of patients with cirrhosis. By comparison, in a systematic review of 118 studies of survival in cirrhosis, 29% corresponded to Child-Pugh class A.<sup>11</sup> Thus, it seems that after initiation of the study, increased awareness about cirrhosis among physicians may have led to earlier diagnosis and therefore a larger proportion of patients who were of Child-Pugh class A. Thus, it seems that in the current study, more patients have milder liver disease at diagnosis and therefore diagnosed earlier than in retrospective studies. At diagnosis, 78 (50%) patients had 1 or more complication, most commonly ascites in 39% of cases. In the Danish study 76% had a complication on presentation<sup>7</sup> and 64% in the recent Swedish study.<sup>19</sup> The incidence of HCC in Iceland has been reported to be among the lowest worldwide. In a retrospective study the annual incidence during 1984–1998 was only 1.08/100,000.<sup>34</sup> In the current study, 12% of patients developed this complication, which is similar to other cohorts with cirrhosis.<sup>11</sup> A recent study from Iceland, published in abstract form, found a significant increase in HCC over time, reflecting increased prevalence of cirrhosis in the country.<sup>35</sup>

### Prognosis

The current study was not designed to assess the prognosis associated with complications that develop over time in patients with cirrhosis. The cohort was probably not large enough to have sufficient power to assess the risks associated with decompensating events in patients with cirrhosis that larger studies have been able to do.<sup>18–21,26,29,36</sup>

During the study period until December 2019, 77 (49%) of patients died, 53% as a result of the complications of the underlying liver cirrhosis. Interestingly, only 2/77 (2.6%) died of variceal bleeding which is much lower than in other recent cohorts with cirrhosis.<sup>16,36–38</sup> Patients with alcoholic aetiology had a better prognosis than patients with non-alcoholic aetiology.

We do not have a clear explanation for this, but it is conceivable that in patients who stop drinking alcohol liver injury can improve, whereas patients with other aetiologies cannot improve liver injury by lifestyle. Access to addiction treatment is very good and free of charge in Iceland. However, the protocol of the study did not include effects of abstinence treatment on prognosis.

A total of 5 (3.2%) patients underwent liver transplantation, which is similar to other cohorts with cirrhosis with similar duration of follow-up.<sup>38</sup> The increased incidence of cirrhosis in Iceland in recent years has led to a significantly increased need for liver transplantation from 2.4 transplants per million population in 1984–1996, 5.2 in 1997–2006, to 8.9 during 2007–2012.<sup>39</sup>

## Conclusions

In summary, a major change in the incidence of cirrhosis was observed in Iceland with a more than 3-fold increase over a

period of <10 years compared with a previous study undertaken from 1994 to 2003. The increase is mostly caused by the increase in nationwide alcohol consumption and an epidemic of obesity and diabetes as well as the late evolution of the HCV infection among people who inject drugs. This study also demonstrates that if thorough evaluation and detailed diagnostic criteria are applied, very few patients have cryptogenic cirrhosis.

With the elimination efforts launched in Iceland with the Treatment as Prevention for Hepatitis C (TraP HepC) program in 2016<sup>40</sup> a decrease in the incidence of cirrhosis caused by HCV is expected. Iceland has historically had strict alcohol control policies. However, access has increased in recent years. The prospects regarding disease burden from NAFLD are uncertain but is likely to increase. With elimination of hepatitis C as a major health threat, continued strict public health approaches in alcohol policy and promotion of lifestyle changes to avoid obesity, cirrhosis is in large part a preventable condition.

## Abbreviations

AIH, autoimmune hepatitis; ALD, alcoholic liver disease; CIF, cumulative incidence function; CRR, competing-risks regression; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease; NAFLD, non-alcoholic fatty liver disease; NALD, non-alcoholic liver disease; NASH, non-alcoholic steatohepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; SHRs, subhazard ratios.

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## Conflicts of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

## Authors' contributions

Conception and design: S.O., E.S.B. Wrote the first draft: S.O. Medical chart review: S.O., E.S.B., O.M.B., J.G.J., S.R. Analysis: S.O., E.S.B., O.M.B., U.B.H., J.G.J. Interpretation of data: S.O., E.S.B., O.M.B., J.G.J., S.R. Critical revision of the manuscript for important intellectual content: S.O., E.S.B., O.M.B., J.G.J. Statistical analysis: U.B.H., S.R.

## Data availability statement

Our data are accessible to researchers upon reasonable request for data sharing to the corresponding author.

## Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhep.2021.100282>.

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